PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 23 July 2007 (23-07-2007)

Applicant's or agent's file reference
9577-59 KAM

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2007/000540	03 April 2007 (03-04-2007)	03 April 2006 (03-04-2006)

International Patent Classification (IPC) or both national classification and IPC
IPC: ***A61K 31/137*** (2006.01), ***A61K 47/38*** (2006.01), ***A61K 9/16*** (2006.01), ***A61K 9/22*** (2006.01), ***A61K 9/36*** (2006.01), ***A61K 9/62*** (2006.01), ***A61P 25/00*** (2006.01)

Applicant
ODIDI, ISA ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[X]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA	Date of completion of this opinion	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	12 June 2007 (12-06-2007)	Connie Kuang 819- 934-3597

Form PCT/ISA/237 (cover sheet) (April 2007)

Box No. I **Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   [X] the international application in the language in which it was filed

   [ ] a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      [ ] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [ ] on paper

      [ ] in electronic form

   c. time of filing/furnishing

      [ ] contained in the international application as filed.

      [ ] filed together with the international application in electronic form

      [ ] furnished subsequently to this Authority for the purposes of search.

4. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. [X] The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.

2. [ ] This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[X] claim Nos. 39 and 42-45

because:

[X] the said international application, or the said claim Nos. 39 and 42-45 relate to the following subject matter which does not require an international search *(specify)* :

Claims 39 and 42-45 are directed to a method for treatment of the human or animal body by surgery or therapy. For the assessment of claims 39 and 42-45 on the question of whether or not they define subject matter that has industrial applicability, no unified criteria exits in the PCT Contracting Sates (Article 33(4), PCT).

[ ] the description, claims or drawings *(indicate particular elements below)* or said claim Nos. are so unclear that no meaningful opinion could be formed *(specify)* :

[ ] the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify):*

[ ] no international search report has been established for said claims Nos.

[ ] a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

[ ] furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

[ ] furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

[ ] pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

[ ] a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	14, 16-17, 26, 29-33, 36 and 54	YES
	Claims	1-13, 15, 18-25, 27-28, 34-35, 37-53 and 55	NO
Inventive step (IS)	Claims		YES
	Claims	1-55	NO
Industrial applicability (IA)	Claims	1-38, 40-41 and 46-55	YES
	Claims		NO

2. Citations and explanations :

The following documents are cited in the present opinion:

D1: WO 2005/074895 A1 (ALEMBIC LIMITED) 18 August 2005 (18-08-2005)

D2: WO 2005/013953 A1 (SYNTHON B.V.) 17 February 2005 (17-02-2005)

D3: WO 2004/096186 A1 (DEXCEL LTD.) 11 November 2004 (11-11-2004)

D4: WO 97/17947 A1 (EDWARD MENDELL CO., INC) 22 May 1997 (22-05-1997)

D1 discloses an extended release pharmaceutical formulation of venlafaxine hydrochloride in the form of mini-tablets in hard gelatin capsule, said mini-tablets having a core and an outer coating. The core of said mini-tablets comprises 40-80% by weight of venlafaxine chloride, 25-45% by weight of microcrystalline cellulose as a diluent, 0.5-10% by weight of polyvinylpyrrolidone as a binder, 1-6% by weight of magnesium stearate/stearic acid as a glidant, 1-6% by weight of talc as an anti-adherent and 1-6% by weight of colloidal silicon dioxide as a lubricant. The said mini-tables are coated with a coating comprising 2-15% of the total weight of the mini-tablets, wherein the coating comprises of 5-90% of a water insoluble polymer (e.g., ethyl cellulose, cellulose acetate, Eudragit™) and 3-50% of a water soluble polymer (e.g., copolyvidone). The method for the preparation of the extended release formulation comprises i) blending the venlafaxine hydrochloride and the diluent (microcrystalline cellulose); ii) granulating the blended mixture with an aqueous or non-aqueous solution of binder and drying it; iii) lubricating the dried granules and compressing into tablets and iv) coating the tablets with an aqueous or non-aqueous dispersion of water insoluble and water soluble components. The extended release composition provides a peak blood plasma concentration of the venlafaxine ingredient at about 10 hours.

D2 discloses an extended release pharmaceutical tablet comprising a core which comprises at least 70% venlafaxine besylate and a coating which comprises at least 50% of an ammonio methacrylate copolymer component, said coating is in an amount within the ranges of 3% to 25% of the weight of said tablet core. The core further comprises 0.2 to 2% of a lubricant (e.g., magnesium stearate), less than 30% of a filler selected from the group consisting of sugars, microcrystalline cellulose, calcium phosphates and mixtures thereof, and a flow enhancer (e.g., silica). Commercially available ammonio methacrylate copolymers include Eudragit® RL series and RS series. The coating can contain other ingredients including other polymers, plasticizers, glidants, surfactants, etc. The extended release tablet allows for controlled release of venlafaxine besylate for at least 12 hours.

D3 discloses an extended release formulation of venlafaxine comprising a core and an outer coating. The core comprises 5-40% by weight of venlafaxine, at least 40% by weight of a filler (e.g., microcrystalline cellulose), at least 5% of a water soluble cellulosic polymer, 0.25 to 5% by weight of a lubricant (e.g., magnesium stearate) and up to about 1% by weight of a flow regulating agent (colloidal silicon dioxide). The coating comprises water soluble cellulosic polymer (e.g., hydroxypropylmethylcellulose) and water insoluble cellulosic polymer (e.g., ethyl cellulose).

D4 discloses direct compressed solid pharmaceutical dosage forms comprising from 40 to 95% by weight of acetaminophen, from 1 to 60% by weight of a direct compression vehicle comprising microcrystalline cellulose and from 0.01 to 4.0% by weight of a lubricant (e.g., sodium stearyl fumarate), and 0.1 to 5% by weight of silicon dioxide. The solid dosage form can also include 0.01 to 4% by weight of disintegrants (e.g., sodium starch glycolate) and less than 10% by weight of fillers (e.g., sucrose, dextrose, lactose, xylitol, fructose, sorbitol, calcium phosphate, etc.). The tablet is coated with a sufficient amount of a hydrophobic polymer or enteric coating material such as Eudragit™ L 100-555, and a hydrophilic coating such as hydroxypropylmethylcellulose. The coating may comprise 0.5 to 30% by weight of the final solid dosage form.

(Continued in the Supplemental Box)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claims 1, 7, 14, 31 and 32 do not comply with Article 6 of the PCT because of the inclusion of "less than about". This expression implies that some undefined values outside of the specified range are intended to be covered, without specifying what those values are. Firstly, it is unclear if the expression refers to a range as a whole or only the last number of the range. Secondly, "about" and "less than" contradict each other as when "about" refers to a range of values above the set number, "less than" infers values equal to or smaller than the set number.

Claim 17 is indefinite and does not comply with Article 6 of the PCT. The expression "at least one (plasticizer/anti-tacking agent)" lacks a proper antecedent basis as claim 16 only refers to one plasticizer and one anti-tacking agent.

Claims 23 and 25 do not comply with Article 6 of the PCT. The inclusions of the following elements: polyethylene glycol (in claim 23) and hydroxyethyl cellulose (in claim 25) multiple times in the list makes the definition of the lubricant and water soluble gellable polymer unclear.

Claim 27 is indefinite and does not comply with Article 6 of the PCT. The inclusion of "cellulose derivative" and "cellulose acetate" in the same selected group causes ambiguity as "cellulose acetate" falls within the scope of "cellulose derivative" in view of the description on page 14.

Claim 28 is indefinite and does not comply with Article 6 of the PCT. The phrase "said at least one water soluble gellable polymer" has no antecedent in claim 27. Claim 27 refers to water insoluble organosoluble polymers. In addition, ethyl cellulose is not a water soluble gellable polymer according to claim 27. It appears that the phrase should read "said at least one water insoluble organosoluble polymer".

Claim 31 is ambiguous and does not comply with Article 6 of the PCT. According to claim 4, at least one component is from about 5 wt% to about 45 wt%. The dependent claim 31 however defines at least one component can be 50 wt% (30 wt% of microcrystalline cellulose + 20 wt% of lactose). This inconsistency between claims 31 and 4 leaves a doubt with regard to the scope of the protection of claim 4.

Claim 31-32 are ambiguous and do not comply with Article 6 of the PCT. According to claims 5-6, at least one glidant and lubricant are both from about 0.5 wt% to about 5 wt%. The dependent claims 31 and 32 define that at least one glidant can be more than 5 wt% ("less than about 10 wt% of silicon dioxide") and at least one lubricant can be more than 5 wt% ("less than about 10 wt% of magnesium stearate"). This inconsistency between claims 31-32 and 5-6 leaves a doubt with regard to the scope of the protection of claims 5-6.

Claim 55 is indefinite and does not comply with Article 6 of the PCT. The inclusion of "The method of any one of claims 1 to 36" causes ambiguity. Claims 1-36 are not directed to a method, instead, they are directed to an extended release composition.

General statements in the description which imply the extent of protection may be expanded in some vague and not precisely defined manner must be avoided. The paragraph on page 7, lines 13-15 implies that the protection sought may be expanded in a vague and not precisely defined manner and thus does not comply with Article 5 of the PCT.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: V

Novelty

Claims 1-13, 15, 18-25, 27-28, 34-35, 37-38 of the present application refer to an extended release composition comprising a coated compressed core, wherein the compressed core comprises at least about 45 wt% of a venlafaxine ingredient, less than about 50 wt% of at least one compound that acts as both a diluent and a compression aid (e.g., microcrystalline cellulose, calcium phosphate, etc.), less than about 10 wt% of at least one glidant (e.g., silicon dioxide, starch, etc.) and less than about 10 wt% of at least one lubricant (e.g., magnesium stearate), and wherein the coating composition comprises 5-55 wt% of at least one water soluble gellable polymer (e.g., hydroxypropylmethylcellulose) and 20-73 wt% of at least one water insoluble organosoluble polymer (e.g., ethyl cellulose, Eudragit™). Claims 39-53 and 55 refer to the use of said extended release composition and the method of making the same. D1 discloses an extended release pharmaceutical formulation of venlafaxine hydrochloride in the form of mini-tablets having a core and an outer coating. The core of said mini-tablets comprises 40-80% by weight of venlafaxine chloride, 25-45% by weight of microcrystalline cellulose as a diluent, 1-6% by weight of magnesium stearate/stearic acid as a glidant, and 1-6% by weight of colloidal silicon dioxide as a lubricant. The said mini-tables are coated with a coating comprising 5-90% of a water insoluble polymer (e.g., ethyl cellulose, cellulose acetate, Eudragit™) and 3-50% of a water soluble polymer (e.g., copolyvidone). It does not matter how magnesium stearate is categorized (glidant in D1 vs. lubricant in the present application) and silicon dioxide (lubricant in D1 vs. glidant in the present application), as long as these excipients are in the composition. As such, both D1 and the above claims define the same compositions as the ingredients are the same. D1 also discloses the same method of making the extended release composition as in the present application. Hence, the subject matter of claims 1-13, 15, 18-25, 27-28, 34-35, 37-53 and 55 lacks novelty over D1 (Article 33(2) PCT).

Inventive step

Lacking novelty, the subject matter of claims 1-13, 15, 18-25, 27-28, 34-35, 37-53 and 55 does not fulfill the requirements of PCT Article 33(3).

The document D1 is considered to be the closest prior art. The teaching of D1 differs from the present invention as claimed in claim 14 in that D1 does not disclose that the coating composition is applied to the core to yield a surface area of less than about 100 mg/cm^2. The subject matter of claims 16-17 differs from the disclosure of D1 in that the coating composition of the present invention can further comprises a plasticizer and an anti-tacking agent. However, it would have been within the purview of the skilled worker to maintain the surface area or to employ the conventional ingredients into the coating composition. Therefore, an inventive step cannot be ascribed to the subject matter of claims 14 and 16-17 (Article 33 (3) PCT).

The extended release composition of claims 26 and 29-33 differs from that disclosed in D1 in that the coating composition comprises hydroxypropylmethyl cellulose and the core comprises at lest one of lactose, mannitol and/or sorbitol as opposed to copolyvidone in the coating and microcrystalline cellulose only in the core of D1. However, it would have been an obvious alternative to use copolyvidone instead of hydroxypropylmethyl cellulose as a water soluble polymer and to substitute microcrystalline cellulose with lactose, mannitol and/or sorbitol as a diluent. As such, an inventive step cannot be ascribed to the subject matter of claims 26 and 29-33 (Article 33 (3) PCT).

Furthermore, the encapsulated coated core as defined in claims 36 and 54 is well known in the pharmaceutical formulation field and the encapsulation of a coated core would have been within the purview of the skilled worker in the art. Hence, the subject matter of claims 36 and 54 lacks an inventive step (Article 33 (3) PCT).

Claims 1-55 lacks an inventive step with respect to D2 in view of D3-D4. D2 discloses an extended release pharmaceutical tablet of venlafaxine ingredient comprising a core and a coating. The core comprises at least 70% venlafaxine besylate, 0.2 to 2% of a lubricant (e.g., magnesium stearate), less than 30% of a filler selected from the group consisting of sugars, microcrystalline cellulose, calcium phosphates and mixtures thereof, and a flow enhancer (e.g., silica). The coating comprises at least 50% of an ammonio methacrylate copolymer component such as Eudragit® RL series and RS series. The teaching of D2 differs from the present invention in that D2 does not disclose that the coating comprises water soluble gellable polymer in addition to water insoluble organosoluble polymer (ammonio methacrylate copolymer). However, the coating composition comprising both water soluble gellable polymer and water insoluble organosoluble polymer is very common in the drug formulation technology, such as disclosed in D3 and D4, wherein water soluble polymer and water insoluble polymer are both used in the coating composition of a drug comprising a core of venlafaxine or acetaminophen. Therefore, an inventive step cannot be acknowledged to the subject matter of claims 1-55 (Article 33 (3) PCT).

Industrial applicability

The subject matter of claims 1-38, 40-41 and 46-55 is considered to be industrially applicable and thus complies with the requirements of PCT Article 33(4).